of essentially chronic disease. Arrest of symptoms, quiescence of lesions, yes; but "cures" in the true sense I do not believe in.

I cannot close this communication without giving my hearty and sincere thanks to my associate worker, Dr. Henry J. Bartle, who has made many practical suggestions, and to Drs. Russell Richardson, S. W. Sappington, John A. Kolmer and H. B. Anderson, respectively pathologists to the Methodist, Hahnemann, Polyclinic and Pennsylvania Hospitals, for their painstaking bacteriologic work on specimens of bile submitted to them.

GLUCOSE AS AN ADJUNCT MEASURE IN THE THERAPY OF PNEUMONIA.

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When the epidemic of pneumonia which followed influenza in 1918–19 struck the army camps we were dealing with 98.2 per cent. of pneumonias at the U. S. Army Base Hospital, Fort Sam Houston, Texas, for which we had no specific therapy. In a series of 819 cases which developed during this season the available data on sputum examinations indicate that we had the small percentage of 1.8 per cent. of pneumococcus type I variety, for which alone antipneumococcic serum type I is available. These data are not complete, due to the fact that in the extreme rush it was impossible to get complete bacteriological reports on all cases; however, they bring forth a true picture of that which is available for reference. In my series of 137 cases reported the incidence of pneumococcus type I was 2.4 per cent., thus still having 97.6 per cent. of cases for which there was no specific therapy.

Such a problem as this naturally raises the question, What is best to do under the circumstances? There being no specific therapy, can we do something in a non-specific way, and what?

In this search for something, something which might help the human organism overwhelmed with infection, I began to use aqueous solution of glucose intravenously. Some other camps had begun to use it; there was a favorable impression as to its efficacy, which seemed justifiable for the procedure. There was practically no literature available on its use in pneumonia.

Naturally there were many questions that arose in my mind at that time, for it was like starting a new experiment in a laboratory, questions which I jotted down at that time in my note-book, for I was going to try to find explanations for these, and answer questions which I can well bring out even now, for no doubt those very questions will arise in anyone's mind who makes an attempt to use glucose therapeutically with an intelligent conception as to its effects. The questions were these:

1. What concentration of glucose should be used?
2. Should it be made up with distilled water or with normal saline?
3. What intervals should be used for its administration?
4. What is the real indication for its use?
5. Is the elimination better in these cases as compared with those who do not get glucose?
6. Does it produce a fall of temperature?
7. Has it any specific effect on osmosis of the lung tissues due to its hypertonicity?
8. Is there any lysis of red blood corpuscles? Can this be demonstrated either by direct smears from blood, by separating the plasma or by the presence of hemoglobinuria?
9. What quantity of glucose should be used at each dose?
10. What are the chills which at times accompany the intravenous administration of glucose due to, and how can they be prevented?
11. What is the explanation of the slowing of the pulse-rate and the improvement of its volume?
12. Why is the patient more comfortable immediately following its intravenous administration?
13. Is there any rise or a fall of blood-pressure?
14. How rapidly can it be given and how slowly should it be given?
15. Does the administration of glucose change the clotting time of blood?
16. Does it stimulate leukocytosis?
17. How much of the glucose is used for bodily nutrition?
18. Why is it advantageous over normal saline?
19. Is extravasation of glucose into tissues at the point of administration alarming?

These then were some of the questions that arose in my mind at the beginning and during the time that I used glucose therapy. For many of these I was able to find an explanation, for others, due to lack of time and inaccessibility to substantial research, I was not. However, I shall take up each one of these questions and present my findings, my attempts toward solving them and give them to you as I solved them.

1 and 2. I found that different concentrations, ranging from 4 to 40 per cent., had been used. The answer then was rather a vague one, and to solve it I set up two series of tubes in the laboratory, one series of glucose, ranging from 1 to 20 per cent., made up in distilled water the other made up in normal saline. To these I added a suspension of human red blood corpuscles and placed them in the

incubator for one hour at 37.5° C., then on ice over-night, making the final reading in the morning. The resut was as follows:

In the distilled water 1 to 5 per cent. hemolysis was present. In the distilled water 5 per cent. and above no hemolysis.

In the normal saline no hemolysis in any concentration: This proved one point to me: as long as I would keep above 5 per cent. solution I was safe so far as the question of hemolysis was concerned, and in the normal saline any concentration could be used.

I compromised on a 10 per cent. solution. 250 c.c. of this, for this was the quantity I used routinely, figured 100 calories, the solution being not thick but convenient for administration. In cases in which the disease was protracted where the question of nutrition came up I used 30 per cent. solution in an attempt to increase the carbohydrate intake to 300 calories per dose.

Erlanger and Woodyatt, in their experimental work, found that one can inject 0.8 to 0.9 gram per kg. body weight per hour for several hours without producing glucosüria. Thus for a man weighing 50 kg. one could inject 50 times 0.9 time 24=1080 grams or 1.08 kg. or over 2 pounds of sugar per day without producing glucosuria. In fact, Woodyatt cites a case in which he has been able to supply 6000 calories per day without producing glucosuria.

This point was a very interesting one to me, for it brought forth a proof that at a moderate administration there was no danger of the glucose passing through the renal filter, thus making one's work a blind issue.

3. In regard to the interval between the administrations I found that more than two doses per day were rarely necessary. In acute cases with high fever and prostration one administration in the morning, after the patient has had his bath and has been fixed up, and one after supper, when he is ready to retire for the night, were all that was found necessary. Following the administration the patient would always fall asleep and have a good rest; he would perspire, following which his temperature would drop 1 to 3°. The rest in itself was a great factor, for to a human machine that is whipped up above its normal capacity if you can give rest and sleep and slow the pulse, reduce the temperature, you have done as much as any conscientious physician can ever hope to do. You have saved the overhead expense which was threatening with bankruptcy. These were the five things which glucose always did for the patient:

1. It made him comfortable.
2. It produced sleep and rest.
3. It reduced the temperature.
4. It increased the elimination through kidneys and skin.
5. It slowed the heart and increased the pulse volume.

When only one dose a day was administered it was always given in the evening, for thus it invariably ensured the patient a good night's rest, and in the morning one could see the bright countenance following a night's rest as compared with one who spent a sleepless night. His fighting chances thus undoubtedly were increased.

4. About the indication for glucose I would say any febrile condition is an indication for its use. When you have fever there you deal with a potential acidosis and a toxemia. This you can combat by the intravenous use of carbohydrates (glucose). You can reduce fever by its administration; you can make an uncomfortable patient comfortable; you help to tide him over. You can do no harm, only good.

5. As far as elimination is concerned, administration of glucose is followed by polyuria. The patient perspires profusely. Thus the two channels of elimination are both reached promptly and effectively.

6. Intravenous administration is followed by a drop of temperature of 1 to 3°. The increased perspiration with evaporation is what makes this drop in the temperature. Renal elimination may be an additional factor here as well.

7. In regard to its osmotic effect on the lung due to its hypertonicity I took up this question with Sollmann, of Western Reserve University. He says: "This is highly improbable. Experimental pulmonary edema is not prevented or influenced in the slightest degree by that factor. Atropin is also useless. The fluid is doubtless due to endothelial injury."

8. To determine whether or not there is any lysis in the blood stream I made the following experiments:

(*a*) I took blood at the beginning, during, at the end and eight hours after the administration of glucose from the same vein into which the needle was inserted (median basilic), some 20 cm. higher up toward the shoulder, making smears and placing the rest in small tubes on ice over-night. This experiment was not successful, as my controls showed lysis while the glucose specimens showed no lysis. Thus faulty technic was undoubtedly used, perhaps boiling of the syringes being at fault. The smears showed no changes of the corpuscles.

(*b*) Several series of urines were collected for one or more voidings before glucose administration, and on each subsequent voiding after the administration, each tested for occult blood, with the following results:

Name.	Specimen before glucose.	Specimen after glucose, successive voidings.	Fehling's test for sugar.
D.	—	— — — — —	—
S.	— —	— — — —	—
C.	—	— — —	—
A.	—	—	—
Lu.	—	—	—
Li.	—	—	—

— negative.

This then would show there is no hemolysis, for if present the hemoglobin would have to be eliminated through the kidneys and give a positive test in the urine.

9. The quantity used can be considerable provided the administration is slow. Even a small quantity of 200 to 300 c.c. if given rapidly may show traces of glucose in the urine, but if given slowly there is practically no limit to the quantity which can be used, for, as mentioned, Woodyatt has been able to give 6000 calories in one day. This is such an overwhelming proof that one cannot question the small quantities of 250 c.c. used here.

I have used 250 c.c., as this quantity is convenient to prepare. One can thus use 8-ounce bottles and prepare a large quantity at one time and keep them on hand, for efficiency of this work depends on preparedness.

The total volume of circulating blood in the human body is approximately 2500 c.c. Injecting into the blood stream 250 c.c. of glucose solution one adds 10 per cent. to the total volume of the circulating fluid. Elimination through the kidneys and later perspiration quickly compensates for it.

10. Chills follow at times the intravenous administration of glucose the same as any intravenous medication, even that of normal saline. Just what they are due to I do not know. Literature does not offer us any definite explanation. They come and we have to deal with them without understanding their pathological physiology.

One can never predict when a chill will come. Frequently a patient will get three to five doses of glucose without any chills, then the next dose is accompanied by a chill, then again he may be free from them for a dose or two and again each subsequent dose followed by one. Or a patient may again start out with a chill following the first dose and not have any more. There has been no regularity whatever to these.

For a while I thought I had found a solution to this question by the use of morphin sulphate, 0.008 gm., and atropin sulphate, 0.00064 gm. When I began to use it for quite a long period I met with no chills. I thought I had made a discovery which could be utilized in chills due even to other causes. But my joy was of short duration, for I began to have them even after these opiate-atropin doses. However, they were not as frequent as formerly. Thus I believe that the morphin-atropin does prevent a certain number of them. Water used for the preparation of glucose solution and perhaps the glucose itself may have something to do with these chills. I used single distilled water.

These chills, however, are not serious. I have seen so many of them, perhaps 200 to 300, in the 1000 to 1200 administrations, and I failed to see any harm come from them. I always tell the patient that if they have a chill not to fear, as it is of no consequence. There is nothing special to do for these chills when they come, except to apply blankets and hot-water bottles to the body.

11. The slowing of the heart-beat and the increase in pulse volume is one of the most striking features of glucose administration. What is it due to? In the first place to the increased volume of the circulating fluids. In the second place to adding fuel to the heart muscle. In the third place through combating acidosis, thus reducing the stimulation of the vasomotor center and the sympathetics. I am sorry that I was not able to have a polygraph to graphically show this point.

12. In my routine administration of glucose I used 250 c.c. of a 10 per cent. solution, with morphin sulphate, 0.008 gm.; atropin sulphate, 0.00064 gm.; tincture digitalis, 1 c.c.

One can say: The rest and the feeling of comfort were due to the opiate. It was not. At the beginning I used no opiate and the same comfort and sleep followed. Opiate, you remember, was used in an attempt to combat the chills and also to add additional comfort and rest. It was the glucose mainly that produced the rest and the comfort.

It was also not the tincture of digitalis which produced the slowing of the heart-beat, for digitalis does not act so quickly. Besides the same slowing and improvement in the pulse volume happened at the beginning when I used no tincture digitalis. This I used to digitalize the heart muscle in case a further use of digitalis were indicated.

It was glucose itself that produced the rest, comfort and sleep through:

(*a*) Additional volume of liquids to a febrile patient.
(*b*) By combating the incipient acidosis.
(*c*) By the increase of elimination.
(*d*) By the decrease of temperature.
(*e*) By strengthening the heart muscle directly and by the supply of carbohydrates to the tissues.

13. In regard to the rise or fall of blood-pressure the few careful readings I took showed a fall of 10 mm. Hg. immediately following its administration, the pressure coming up again to normal in forty-five to sixty minutes, as seen in the accompanying Chart I.

The removal of 5 c.c. of blood per kg. of body weight does not influence the blood-pressure (Macleod). From this I reason that if the removal of 5 c.c. of blood per kg. body weight does not influence the blood-pressure the addition of 5 c.c. of fluid per kg. body weight should also have no effect on blood-pressure. Thus, taking a man weighing 50 kg. and adding 5 c.c. of fluid, 50 times 5 = 250 c.c., which one ought to be able to add to the circulation without producing any effect. My blood-pressure readings seem to bring out this point.

14. As to the rapidity of administration. Naturally one cannot use too much speed for fear of cardiac dilatation. This applies especially to weakened hearts. I take fifteen to twenty-five minutes

for the administration of the 250 c.c. glucose. Too slow a procedure is also not advisable unless the receptacle can be kept at constant temperature, which is very impracticable at a bedside and quite unnecessary. All that is necessary is to allow for the cooling of the liquid before its entrance into the vein. I have made the following observations in order to show the amount of cooling during the procedure:

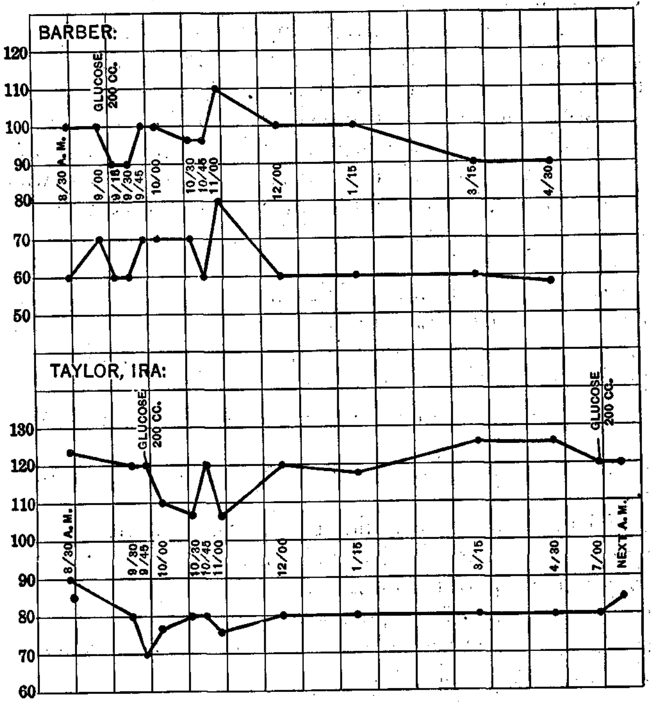


CHART I.—Observations on blood-pressure changes during intravenous administration of glucose.

A 250 c.c. bottle filled with glucose solution, a 3-way stopcock and a 10 c.c. syringe were used, the bottle being kept at a constant temperature. The exit temperature was measured from a No. 20 gauge needle in a test-tube.

Glucose, per cent.	Reservoir temperature.	Exit temperature.
10	37.5° C.	27° to 28°
10	78.0° C.	57° to 58°
30	37.5° C.	28° to 29°
30	68.0° C.	54° to 55°

From this one can see readily there is a considerable cooling of the liquid during the process of administration, so that the solution should be considerably above the body temperature and not as usually is advocated and practised, at body temperature.

15 and 16. I have not made any determinations as to the clotting time of blood, neither that of the leukocytic stimulation.

17. All of the glucose is used for bodily nutrition. Repeated tests for sugar in the urine failed to show it in carefully collected specimens except once when a trace was found. When Woodyatt could administer 6000 calories without any production of glucosuria one naturally would not expect to find any from 100 to 300 calories.

18. In administration of normal saline one adds to the bodily fluids. This is true thus far. One does nothing more. With glucose you not only supply fluids, but you also supply food, fuel and that which you need for combating the incipient acidosis present. What does saline do to acidosis? It aggravates it (Macleod), and this is the point in question. With glucose you do all that a saline can do and a whole lot more.

19. Extravasation of glucose into the tissues is not alarming; it does no harm, the same as saline extravasation into the tissues.

I made an attempt in some cases to see what the concentration of glucose in the blood stream was just before and right after the administration of 250 c.c. of 10 per cent. glucose solution. The readings are as follows:

Name.	Date.	Before, per cent.	After, per cent.	Six hours later.
Mc.	November 27	0.130	0.190	
R.	November 28	0.146	0.269	
	November 29	0.11	0.22	0.104
P.	November 30	..	0.232	
M.	November 30	0.076	0.24	
	December 1	0.11	0.194	
S.	December 2	0.098	0.19	
W.	December 4	0.108	0.252	
P.	December 3	0.18	0.248	
P.	December 3	0.07	0.4	
	December 4	0.1	0.2	
M.	December 7	0.076	0.29	
R.	December 10	0.1	0.204	
	December 11	0.16	0.256	
	December 12	0.18	0.204	
	December 13	0.114	0.268	
B.	December 11	0.104	0.264	
	December 12	0.18	0.204	
T.	December 9	0.128	0.228	
Mc.	December 14	0.12	0.328	
	December 16	0.16	0.216	
A	December 5			

10.30 A.M.—Sugar before glucose, 0.160 per cent
10.50 A.M.— " after " 0.232 "
11.50 A.M.— " " " 0.124 "
12.50 P.M.— " " " 0.152 "
1.50 P.M.— " " " 0.080 "
2.50 P.M.— " " " 0.080 "

To show the effect on pH before and after the administration of glucose the following determinations were made on blood:

Name.	Date.	pH before.	pH after.
R.	December 13	7.6	7.5
B.	December 12	7.1	7.1
Mc.	December 14	7.6	7.3
	December 16	7.4	7.4
W.	December 31	7.5	7.4
	January 1	7.4	7.2
G.	January 1	7.6	7.4
R.	January 10	7.5	7.3

The degree of acidosis is so slight that the variation naturally is small also. However, there is a definite decrease, as the figures show.

For the physiological action of glucose and its fate in the tissues I will cite Erlanger and Woodyatt:

When a single dose of glucose is injected there is a temporary increase of sugar in the circulation. The injected sugar passes rapidly out of the blood into the tissues. During its stay in the vessels the blood volume rises and a state of hydremic plethora develops, owing, doubtless, to the binding of water by the extra glucose in the vessels. This is shown by the fall of the hemoglobin percentage and a coincident fall in the blood-sugar percentage following the initial rise. These facts have been demonstrated by Brasol and confirmed and amplified by Biedl and Kraus. Similarly during the period of absorption following the alimentary administration of glucose there is at first a rise and later a return to normal of the blood-sugar percentage, and simultaneously with the latter a fall in the hemoglobin percentage.

You can inject 0.8 to 0.9 per kg. of body weight per hour for several hours without producing glucosuria. With the injection of 0.9 or more grams per kilogram per hour glucosuria develops and the rate of sugar excretion bears a definite relation to the rate of injection. During a sustained intravenous glucose injection at the sugar tolerance rate or below it glucose passes from the blood into the tissues and there undergoes chemical polymerization, oxidation, etc., at the same rate as that of injection. There is no material accumulation of glucose in the tissues. Injections at a subtolerant rate thus have a tendency to increase the glucose content in the blood without producing any appreciable increase in glucose in the tissues. The result is a disproportionate increase of the power of the blood to hold water and a state of hydremic plethora develops and presumably persists as long as the injections are sustained. The water held by the blood must come from the tissues or from the injection site or both. If the water injected with the glucose is not sufficient to satisfy the glucose in the blood some water will flow into the blood stream from the tissues. When the glucose injection is stopped and the last of the injected glucose passes into the tissues the water previously held by the blood is suddenly discharged into the urine. This whole phenomenon differs essentially from that obtainable with inorganic salt solutions, because such salts when injected also pass into the tissues, but when once there are not destroyed. There is therefore a possibility of salt accumulation in the tissues holding water there and in part counteracting effects of the salt in the blood stream. With sustained intravenous injections of glucose at rates higher than 0.8 to 0.9 gm. per kg. per hour the glucose utilization fails to keep pace with that of the injection and the tendency is toward some accumulation of unchanged glucose. If the kidneys are functionating actively this glucose appears on the urinary side of the renal membrane and tends to collect water in this locality, probably for the same reason that glucose in the blood produces hydremia. This tendency is expressed as polyuria. Now if the diuresis exceeds water administration, water will flow from the tissues to the blood and thence to the urine, and hydremia will be sustained as long as the water supply is adequate. But if the kidneys do not function in this way most of the unchanged fraction of glucose injected remains in the body and tends to behave like a salt, causing accumulation of water in the tissues and body spaces wherever it may go. In shock cases the secretion of urine is likely to be impaired. Accordingly the most rational application of an intravenous glucose injection in shock would appear *a priori* on theoretical grounds to consist in long, sustained, uniform injections of subtolerant doses.

Author's Routine: 250 c.c. of a 10 per cent. aqueous solution of glucose are given b. i. d. or t. i. d. as indicated, 30 per cent. solution where there is a question of nutrition. Only chemically pure glucose should be used and distilled sterilized water. A good plan is to prepare larger quantities and use 250 c.c. (8 oz.) bottles, cotton stoppers, paraffin paper over these well down over the neck of the bottle, so that one would always have a sterile lip on the bottle to pour the solution from. Sterilize by boiling or autoclaving, then store on ice.

The method of administration is that of any arsphenamin method. Either a tube reservoir or else a 3-way stopcock with a 10 c.c. syringe can be used. In case of the latter the original bottle serves as a reservoir. The latter is more practical for private work, the first for hospital use.

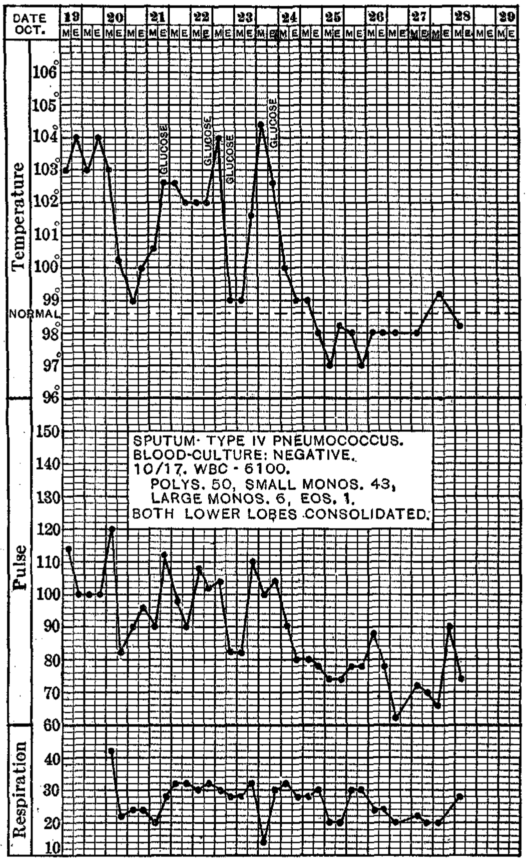
Use as small a needle as you can. The smaller a needle the easier it is to enter the vein.

It is advisable to administer all the medication in glucose. I use routinely:

Tr. digitalis	1.00000 c.c.
Morphin sulph.	0.00800 gm.
Atropin sulph.	0.00064 gm.
Glucose, 10 per cent.	250.00000 c.c.

The first is to digitalize the heart muscle and the latter to secure rest and also to prevent chills which sometimes follow any intravenous medication. The solution is heated to about 50° C., and from fifteen to thirty minutes allowed for its administration.

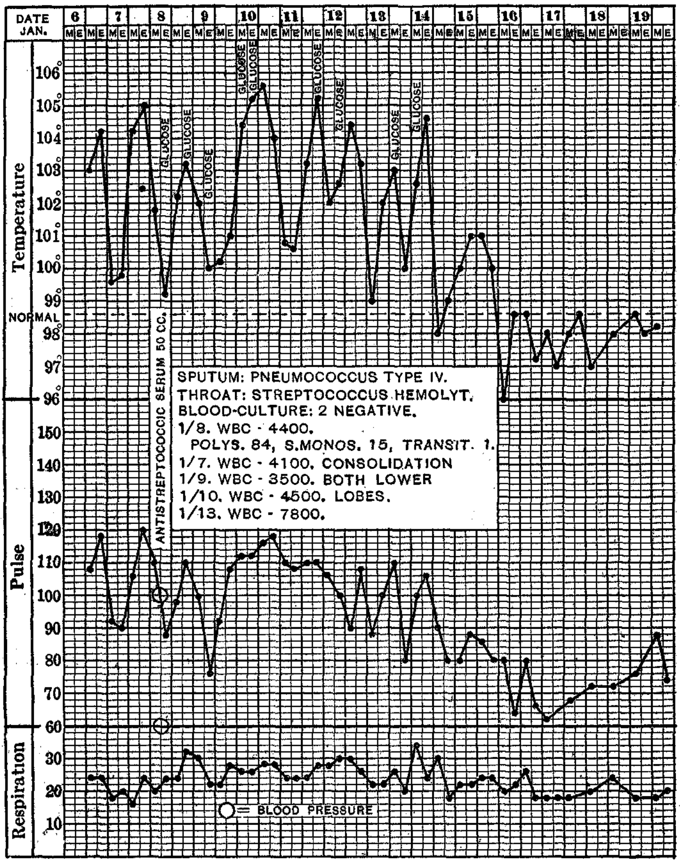
Remember that an ounce of prevention is worth a pound of cure. Thus do not wait with the glucose administration until the patient is nearly dead and then expect any miraculous result from it.



SPUTUM· TYPE IV PNEUMOCOCCUS.
BLOOD-CULTURE: NEGATIVE.
10/17. WBC - 6100.
POLYS. 50, SMALL MONOS. 43,
LARGE MONOS. 6, EOS. 1.
BOTH LOWER LOBES CONSOLIDATED.

CHART II

Begin early and thus preserve the patient's strength, his natural resources, since you can do nothing specific so far as cure is concerned. Do not let the patient suffer. I think that the morphinphobia which is so impressed on the medical student has done a lot of harm when we are dealing with acute infectious diseases. The tendency is to use morphin only as a last resort, when one can see that the patient cannot live, to make his end easy. This is one of the greatest mistakes in therapy. It should be used early, to save the patient and his natural resources, his fighting power, that he may win the victory over the infection and not be let suffer and uselessly spend his energies. It is nothing less than stupid to think that a patient will become a drug addict from the three to ten doses of morphin which he does not even know that he is getting in the glucose, but thinks that it is the glucose alone giving him the relief.



SPUTUM: PNEUMOCOCCUS TYPE IV.
THROAT: STREPTOCOCCUS HEMOLYT.
BLOOD-CULTURE: 2 NEGATIVE.
1/8. WBC - 4400.
POLYS. 84, S.MONOS. 15, TRANSIT. 1.
1/7. WBC - 4100. CONSOLIDATION
1/9. WBC - 3500. BOTH LOWER
1/10. WBC - 4500. LOBES.
1/13. WBC - 7800.

CHART III

While febrile, the patient should receive all the liquids and nourishment he will take. Fruit juices, too, are of great value.

Enemas, baths, etc., naturally should always precede the intravenous administration. After this the patient should be left perfectly quiet to rest and to sleep. A natural rest and sleep do more for the patient than all the medical armamentorium in our possession.

Our problem in pneumonia is much the same as any problem of surgical infection. What does a surgeon do? He abides by the following principles:

1. Rest.
2. Supply of liquids and food.
3. Drainage.

Our infection is widely spread through the lung tissues, but the patient is absorbing from them just the same as the surgical case is from his area of infection. The toxic products are getting into the circulation, causing toxemia, ever, prostration and death. Through morphin and glucose you furnish rest. Through glucose you supply liquids and food to the body. The third cannot be accomplished medically. Our principle then is just the same and we can well afford to follow the surgical lead.

CONCLUSION. From the above discussion and data one can readily gather the following:

1. That the administration of glucose is without danger provided any reasonable care is used. In the 1200 administrations not a single accident developed.
2. That the patient is made comfortable and sleep is provided for him. Through this the whole organism is strengthened for the prolonged fight against the infection.
3. That the temperature is lowered.
4. That nutrition is provided for the overtaxed heart muscle without having to go through the ordinary digestive processes, storage in the liver as glycogen and reconversion into glucose again before it can be burned by the tissues. 100 to 300 calories is thus supplied to the body per each dose.
5. That a considerable amount of fluid is provided for the circulation. This together with the preceding slows the heart, producing thus artificial rest.
6. That the elimination through the kidneys and the skin is increased.
7. That practically all the medication can be supplied in the glucose, thus a much more accurate dosage can be depended on.
8. That the antipneumococcic serum type I or the antistreptococcic serum, the antitetanic serum, can be administered in this glucose medium. This is far superior to saline, for glucose will do much more than saline, thus being a much more rational medium to use as a diluent for any intravenous medication.
9. That the use of glucose is strictly a physiological measure and is to be used as such.[1]

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[1] In private communication with Dr. H. O. Mosenthal, he brings out the fact that commercial glucose is preferable to the chemically pure product, which in its purification contains traces of acetic acid, and he thinks that these traces of the acetic acid have something to do with the chills that follow. His experience has been that after he had abandoned the use of the chemically pure product and resorted to commercial glucose, no chills followed. This is worth bearing in mind and publishing the results of such an investigation in the future.